Dockets Management Branch (HFA-305),
Food and Drug Administration,
5630 Fishers Lane, rm. 1061,
Rockville,
MD 20852

00D 1392 '00 DEC 13 12:15

Dublin, 8th December 2000

TIBOTEC

Tibotec Pharmaceuticals Ltd.
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Ireland
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Fax + 353 1 820 80 82

Dear Sir or Madam,

Re: Guidance for Industry, Botanical Drug Products – Comments
Docket No. 00D-1392, CDER 97113

On behalf of TIBOTEC, I wish to provide you with comments on the draft Guidance for Industry, Botanical Drug Products, of August 2000.

Introduction

TIBOTEC is an emerging, globally oriented pharmaceutical company, focused on discovering and developing superior pharmaceuticals for unmet medical needs. The scientific background of the company lies in the field of HIV infection and AIDS, infectious diseases (e.g. Leishmaniasis and tuberculosis), cancer and Alzheimer's disease.

TIBOTEC's headquarters and European R&D centre are located in Mechelen, Belgium. The US R&D laboratory, TIBOTEC, Inc., is located in Rockville, Maryland, USA. TIBOTEC's commercial activities are coordinated through TIBOTEC Pharmaceuticals Ltd., located in Dublin, Ireland. TIBOTEC Group NV was founded in 1994 by Rudi Pauwels, PhD, and Carine Claeys, pharmacist, with the objective of performing drug discovery and pre-clinical drug profiling in the focus areas. Paul Stoffels, MD, joined in 1997, when the target was extended to the establishment of an integrated pharmaceutical company. Dr. Pauwels authored the first paper describing the non-nucleoside HIV Reverse Transcriptase inhibitors (TIBO-compounds; *Nature 1990*).

TIBOTEC leverages intensive R&D efforts in AIDS drug discovery, resistance biology, and drug discovery technologies, such as ultra high-throughput screening, structure-based drug design and bio-informatics. The company has combined automation with intelligent image analysis methods to enable high-content screening of chemical libraries in cellular assays using a novel ultra high-throughput format. Drug discovery technologies, including structure-based drug design methods, are all aimed at increasing the speed and efficiency of target selection, assay design, and lead optimization.

Comments

In general, we are in agreement with the Guidance for Industry, Botanical Drug Products and we are pleased that such guidance is being drafted and will soon be available to industry.

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Nevertheless, we would like to express our concerns regarding the terms 'highly purified' and 'botanical drug substance' as used throughout the document. In the annex to these comments is an example of a purified botanical drug substance, upon which our concerns are based. In our opinion, this mixture should be considered as a botanical.

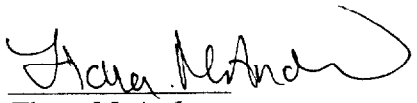
From the guidance, however, it is unclear given the level of purification as outlined in the annex, whether this botanical substance or mixture of substances is indeed considered a 'botanical'. More specifically, it is not clear if the unspecific term '.... or other similar process.' (as used in the sentence beginning 'It is prepared.....' In the definition for a Botanical Drug Substance) would apply to purification techniques such as those outlined in the example.

We therefore would like to see further clarification of the terms 'highly purified' and 'botanical drug substance' as used in this document with regard to specific stages and methods/techniques of processing.

We hope that the Centre for Drug Evaluation and Research will find these comments useful and consequently we hope to see them reflected in the final Guidance for Industry, Botanical Drug Products document.

Please contact me should you require more information or clarification.

Yours sincerely,



Fiona McAndrew
Regulatory Affairs Officer

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ANNEX

PURIFIED BOTANICAL DRUG (SUBSTANCE)

1. INTRODUCTION

The composition of a botanical drug may vary from very complex and poorly defined (an extract) to a (partially) defined purified extract using different purification techniques.
The product referred to in the comment document is a purified botanical drug obtained by the process described in more detail below.

2. PROCESS

Basically the production process consists of 3 steps:

- solid-liquid extraction of plant leaves
- liquid-liquid extraction and washing (purification)
- additional purification

The result of this process is a (partially) defined botanical extract.

2.1. Extraction

Dried and milled plant leaves are extracted with ethanol 70° by repeated maceration overnight and percolation, at a ratio plant material:alcohol of 1:5.

2.2. Initial purification

The ethanolic botanical extract is concentrated and purified by consecutive liquid-liquid extractions. These extractions facilitate the removal of lipid constituents (water//hexane) and water-soluble components (water/butanol). The semi-purified botanical extract is obtained by precipitation in aceton and washing with other organic solvents.

2.3. Purification

The final purification is performed using one or more different purification techniques.
Tannins are removed on a gel (Sephadex).
Filtration on a reversed phase packing possibly removes more polar and/or more lipophylic fractions.

Depending on the technique(s) used, a purified extract with a different composition can be obtained. The purified extract contains at least 6 identified active compounds and a matrix consisting of related compounds (unidentified but structurally related compounds) and other unknown compounds (such as inorganic salts).

DHL WORLDWIDE EXPRESS

Shipment Airwaybill

(Non negotiable)

450 2689 236

Quote this shipment number in an enquiry

ORIGIN | DESTINATION: G A I

1 From (Sender)

Account no.: [illegible]

Sender's name: Fiona McAndrew

Sender's reference *first twelve characters will be shown on invoice*

...OTEC PHARMACEUTICALS
UNIT 4A
BLANCHARDSTOWN CORPORATE PARK
BLANCHARDSTOWN DUBLIN 15

Postcode:

Phone / Fax / Telex: 353 1 8208114

2 To (Receiver)

Food + Drug Administration
Dockets Management Branch (HFA-305)
5630 Fishers Lane, Rm 1061
Rockville, MD 20852

Postcode: 20852

USA

Contact person: Yuan-Yuan Chiu

Phone / Fax / Telex: 301 827 4573

5 Sender's authorisation and signature

I/we agree that DHL's standard terms apply to this shipment and limit DHL's liability. The Warsaw Convention may also apply (see reverse).
I/we understand that DHL does not transport cash or dangerous goods (see reverse).

Signature: [signature] | Date: 8/12/00

3 Shipment details

Not all payment and service options are available in all countries.

Services

- [x] DOCUMENT
- [ ] WORLDWIDE PARCEL EXPRESS *all declarables*
- [ ] INTRA EC *(in free circulation)*
- [ ] EXPRESS DOCUMENT
- [ ] DOMESTIC
- [ ] WORLDMAIL Airmail/Printed Matter *specify one*
- [ ] OTHER SERVICE .... *specify*

Transport charges
If left blank sender pays transport charges

- [x] Sender
- [ ] Cash / Cheque / Credit Card
For approved customers only
- [ ] External Billing Agreement
- [ ] Transport Collect

Shipment insurance
- [ ] YES

Full description of contents

Documents

International Worldwide Parcel Express shipments only

Declared Value for Customs *give currency*	Sender's VAT / GST no.
Harmonised commodity code *if applies*	Receiver's VAT / GST no. or EIN / SSN

Type of export: [ ] PERMANENT [ ] REPAIR/RETURN [ ] TEMPORARY

Destination duties / taxes *If left blank receiver pays duties / taxes*
[ ] Receiver [ ] Sender [ ] Other .... *Specify destination approved account number*

4 Size and weight

No. of pieces	Weight
	.5 kg

Dimensions *cm L x W x H*: x x

VOLUMETRIC/CHARGED WEIGHT: . kg

CODES	CHARGES
	Services
	Special
	Insurance
	Other /VAT
CURRENCY CODE	TOTAL

TRANSPORT COLLECT STICKER No.

PICKED UP BY
Route No. DA12
Time 1205
Date 11.12.00

Consignee / Parcel copy